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Predictors of morbidity and mortality in COVID-19

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Abstract. – The mortality of COVID-19 patients is increasing in logarithmic fashion and is mostly observed in older age people and patients having history of chronic ailments like chronic obstructive pulmonary disease (COPD), hypertension, diabetes, cardiovascular & cerebrovascular dysfunction, compromised immunity, renal comorbidities, hepatic, obesity problems etc., and recently investigated thrombotic complications. The molecular underpinnings linking the chronic human diseases with COVID-19 related morbidity and mortality are evolving and poorly understood. The aim of the present review is to discuss the mortality and morbidity in COVID-19 in relation to preexisting comorbidities across the globe, upcoming molecular mechanisms associated with expression profile of ACE2 and viral load, evolving pathophysiology of COVID-19 with special reference to thrombotic complication ('Storm of Blood Clots') and related predictive markers. The levels of plasminogen/plasmin in comorbid diseases of COVID-19 have been elaborated in the framework of risk and benefits of fibrinolysis in COVID-19. We have also attempted to discuss the puzzle of prescribing ARBs and ACEI drugs in COVID-19 management which are routinely prescribed for the management of hypertension in COVID-19 patients. A focused discourse on risk of cardiovascular complications and diabetes in concert with COVID-19 pathogenesis has been presented along with dynamics of SARS-CoV-2 induced immune dysfunctions in COVID-19 patients.

Key Words:
COVID-19, Pathophysiology, Chronic comorbidities, Molecular predictors, Biomarkers, Mortality and morbidity.

Introduction

Since the first report of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection from Wuhan, Hubei, China on 31st December 2019, the spread and infected cases of coronavirus disease 2019 (COVID-19) are increasing in logarithmic fashion. In the present state-of-the-art, the outbreak of pandemic caused by SARS-CoV-2 is not only a challenge for national health systems, but it has equally forbidden the economic and social life of people across the globe. As accessed on 10th January 2021, according to World Health Organization, over 106.32 million people are suffering from COVID-19 with a toll of over 2.32 million COVID-19 related deaths, with maximum cases of infections and related deaths from USA (https://covid19.who.int). The clinical spectrum of the COVID-19 is very broad and is evolving with variety of novel clinical presentations. Series of clinical and epidemiological investigations being carried out across the world are unraveling different dimensions of pathophysiology of COVID-19, which perhaps will help to tailor the suitable treatment modalities as the current therapeutic approach is mainly supportive in nature[1].

In the early phase of clinical observation, respiratory failure was attributed as a major cause of morbidity and mortality of COVID-19 patients[2], however, the upcoming clinical and epidemiological data links it with patients having preexisting history of hypertension[3], chronic obstructive pulmonary disease[4,5], diabetes[6], coronary heart disease[7], cerebrovascular disease[8], and kidney comorbidities[9] have worse clinical outcomes when infected with SARS-CoV-2. In the second phase of clinical observation, vascular thrombosis has been observed in many patients and has been speculated to be associated with COVID-19 mortality[10]. Moreover, the demographic characteristics of the population of different countries especially the age of the COVID-19 patients is also being considered as a risk factor for COVID-19

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infection and related mortality[11]. The link of malignant conditions with COVID-19 mortality is under debate owing to a smaller number of patients[12].

The voluminous clinical observations made so far is from the China Center for Disease Control and Prevention. In their report of 44,000 patients who tested positive for COVID-19, the older age and comorbidities of cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and malignancy were all associated with higher risk of death[13]. A retrospective cohort study[14] from Wuhan, China has observed that the most common comorbidities of COVID-19 patients were associated with hypertension (30%), diabetes (19%), and 8% coronary heart disease. Preliminary estimates of the prevalence (from February 12-March 28, 2020) of selected underlying health comorbidities of the COVID-19 patients from USA, indicates that, the severity of the COVID-19 illness is strongly associated with chronic ailments, such as diabetes mellitus, chronic lung disease, cardiovascular disease (CVD) etc. and many times the deaths in such persons might not be recognized as being directly linked with COVID-19[15]. A detailed chart review of 355 COVID-19 patients who died in Italy, revealed that the patients were mean age of 79.5 years and had comorbidities of diabetes (35.5%), ischemic heart disease (30%), active malignancy (20.3%), atrial fibrillation (24.5%), dementia (6.8%), history of stroke (9.6%), with a mean number of preexisting diseases of 2.7[16]. Until March 11th, 2020, according to the Istituto Superiore di Sanità, Italy, which had over 12,462 confirmed COVID-19 patients and over 827 deaths, the mean age of patients died in Italy was 81 years and more than two-thirds of these patients had preexisting chronic ailments like diabetes, CVD, cancer, and were also former smokers[17].

Series of COVID-19 rapid risk assessment updates for EU/EEA and the UK published by European Centre for Disease Prevention and Control (ECDC) consistently links the severity and ICU hospitalization of COVID-19 patients with diabetes, hypertension, chronic lung disease, CVD, immunocompromised condition, renal and liver disease. The countrywide data published by ECDC, showed that the hospitalised COVID-19 ICU patients from USA (32%), Sweden (23%) Italy (17%) and Spain (17%) had prehistory of diabetes. Similarly, the hypertension was found to be a more prominent factor in ICU admitted patients from Italy (49 %) and Sweden (34%), while the ICU patients from Spain (30%), USA (23%), Italy (21%) and Sweden (11%) were suffering from comorbidities of CVD[18]. The consolidated data of 1578 hospitalized severe COVID-19 cases from 23 European countries, including UK revealed that the severity of hospitalized cases was closely associated with cardiac disorder (excluding hypertension; 21.7%), diabetes mellitus (17.4%), chronic lung diseases (excluding asthma; 10.5%), renal disease (6.5%) and hypertension (6.4%). While the chronic comorbidities related to neuromuscular & neurological disorder, malignancy, HIV or other immune deficiency, asthma, liver disease, hematological disorders were less than 4%[19].

In general, the most commonly observed comorbidities in COVID-19 patients are hypertension followed by diabetes, chronic cardiovascular disorders, cerebrovascular diseases, COPD, and chronic kidney dysfunction[14]. Better understanding of the clinical manifestation of severity of COVID-19 progression in concert with pathogenesis of SARS-CoV-2 and pre-existing comorbidities will provide an important insight which perhaps can be explored for tailoring novel treatment approaches and designing target oriented therapeutic agents against COVID-19.

Evolving Pathophysiology of COVID-19

The clinical observations described above clearly correlate the mortality and morbidity of COVID-19 patients with pre-existing chronic health comorbidities, however, limited knowledge is available towards the pathophysiological markers linking the clinical manifestation, severity of illness, morbidity and mortality of COVID-19. In the present state-of-the-art, the pathophysiology of COVID-19 is investigated at different levels. Angiotensin converting enzyme 2 (ACE2), being a receptor and an entry point molecular player for SARS-CoV-2, is widely discussed in the mainstream COVID-19 pathogenesis. Also, the first investigations are centered on molecular players in aggravation of SARS-CoV-2 induced respiratory pneumonia, vascular perturbations leading to lung, cardiovascular, neurovascular and other organ failures, and poor clinical outcomes due to impaired immune functions.

Why the Expression Levels of ACE2 Are in the Limelight of COVID-19 Pathogenesis?: A Demon or Angel?

The S (spike) protein of SARS-CoV-2 which has very strong binding affinity (10 to 20-fold higher than SARS-CoV) with angiotensin con-

verting enzyme 2 (ACE2), allows the entry of virus inside the host cell by a process of endocytosis in a manner akin to HIV. The proteases, such as TMPRSS2 are involved in S protein priming and cleavage of the spike, while the proteases, such as Furin, subsequently release the spike fusion peptide, and the cellular virus enters through an endosomal pathway[20]. The normal lung tissue biopsy observations revealed that over 83% of ACE2-expressing cells were belonging to alveolar epithelial type II cells (AECII). Moreover, the gene ontology enrichment experiments showed that the ACE2-expressing AECII cells have high levels of gene expression which are involved in viral genome replication, life cycle, and assembly etc.[21]. This indicates that the ACE2-expressing AECII cells make lung tissue more susceptible for SARS-CoV-2 infection. Apart from pulmonary expression of ACE2, the ACE2 receptor is also expressed in many extra pulmonary tissues/organs, such as heart, kidney, enterocytes, pancreas, endothelium, intestine and macrophages and equally predispose these cells/organs for the entry of SARS-CoV-2. Interestingly, However, ACE2 is not expressed in the spleen, lymph nodes, thymus, bone marrow, and B and T lymphocytes, and macrophages[22,23].

In a renin-angiotensin system, ACE2 has counter acting functions against angiotensin II (AngII) which is generated by ACE1. The catalytic action of ACE2 converts Ang I to Ang-(1-9) and Ang II to Ang-(1-7). Preferentially, ACE2 has 400-fold higher affinity with Ang II as compared to Ang I[24]. Furthermore, AngII activates AngII type 1a receptor (AT1R) and induces vasoconstriction, fibrosis, and salt retention, while on the other hand Ang1-7 binds to mas oncogene receptor and stimulates vasodilatation, acts as anti-inflammatory, antifibrotic and suppresses cell growth. The balanced regulations of ACE2/angiotensin 1-7/mas receptor axis and ACE/angiotensin II/AT1R axis is pivotal for maintaining the functional integrity of various organs. However, the ACE/angiotensin II/AT1R axis is excessively activated in a variety of comorbidities and disorders, such as hypertension, heart failure, cardiac hypertrophy and other cardiovascular disorders[24].

ACE2 is highly expressed in the heart and lung and plays a pivotal role in cardiovascular and immune systems[25]. It also plays an important role in heart function, hypertension and diabetes. As ACE2 is a functional receptor for entry of SARS- CoV-2, the virus invades mainly alveolar epithelial cells and causes respiratory pneumonia symptoms. The severity of respiratory symptoms in patients with cardiovascular disorders might be associated with increased expression and secretion of ACE2 as compared with healthy humans[26]. Apart from heart and lungs, the ACE 2 is expressed on several tissue organs, such as the adipose tissue, kidney, intestine, and blood vessels especially endothelial cells; perhaps these tissue/organ specific expressions of ACE2 may explain the aggressive occurrence of pneumonia and bronchitis in critically ill COVID-19 infection. This widespread expression of ACE 2 in the human body and its high avidity for the SARS-CoV-2 spike (S) protein might predispose the tissues and organs for the massive entry of virus and thereby initiate multiple clinical adversities including the acute respiratory syndrome, renal failure, intestinal perforation, and disseminated vascular thrombosis etc.[27,28] (Figure 1).

While discussing the link of ACE2 expression and diabetes mellitus, there is sound preclinical evidence which demonstrated the elevated levels of ACE2 expression in the lung, kidney, heart, and pancreas of the rodent diabetic animal, while the insulin administration was found to be associated with attenuation of ACE2 expression levels[29,30]. Several preclinical animal model studies have also demonstrated that, the hypoglycemic agents like liraglutide (agonists of glucagon-like peptide-1: GLP-1), thiazolidinediones (pioglitazone), and antihypertensive drugs, such as ACE inhibitors, and statins up regulate the expression of ACE2[31-33]. Using a phenome-wide Mendelian randomization, the researchers found that diabetes was causally associated with elevated levels of ACE2 in lung[34]. Perhaps, there is a scope to extrapolate and relate the outcome of above studies to pathophysiology of COVID-19, wherein the elevated levels of ACE2 might be associated with increasing the susceptibility of human organs towards SARS-CoV-2 infection, on the other hand, the reduced levels of ACE2 might contribute to tissue/organ damage owing to increased titer of ACE-2[24]. Moreover, the human endocrine pancreas is known to express ACE2 and thereby allow the entry of SARS-CoV-2 in islets and cause perturbations in β-cells function, leading to acute hyperglycemia and transient type 2 diabetes[35] (Figure 1).

ACE2 mediated cardio- and neurovascular comorbidities are one of the growing concerns in the management of COVID-19. It has been well established that ACE2, a doorstep portal for viral entry is also highly expressed in heart tissues[36,37].

Endothelial cells and pericytes are the building blocks of vascular architecture, and ACE2 receptors are known to be expressed by endothelial cells[38] and pericytes[39]. High expression of ACE2 in pericytes might lead to development of microvascular dysfunction[40]. More precisely, single-cell atlas of the human heart showed that pericytes have high levels of ACE2 expression in the heart, explaining greater possibilities for acute coronary syndromes[39,41]. Similarly, the expression of ACE2 on endothelial cells at the junction of blood-brain barrier may facilitate the entry of SARS-CoV-2 into the central nervous system leading to neurovascular damage. Perhaps, the ACE2 mediated cardiovascular injury can be attributed with dysfunction of endothelial cells and pericytes, however, the molecular players in endothelial cell and pericyte mediated vascular derangements in COVID-19 are not known (Figure 2). Moreover, ACE2 is overexpressed in heart failure and arterial hypertension, suggesting a plausible reason for a higher infectivity of virus and a higher mortality in patients with heart failure[42]. Furthermore, the administration of anti-hypertensive ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) may result in a compensatory increase in tissue levels of ACE2 and theoretically (no empirical evidence in humans) may increase the susceptibility towards SARS-CoV-2 infection. On the other hand, once SARS-CoV-2 enters through ACE2 into the host cell, it subsequently downregulates the levels of ACE2 expression and the low titer of enzyme may not be effective in providing protection to tissue/organ damage. Perhaps the noncompeting angiotensin II accumulation may be a cause for tissue/organ injury in COVID-19[38]. In this context, the levels of ACE2 are in a paradigm of 'Demon or Angel?' However, the 'Demon' gesture of ACEIs and ARBs induced ACE2 and increased susceptibility to SARS-CoV-2 infection is yet to be demonstrated in human subjects[43].

There is a growing interest in measuring the circulating ACE2 levels as a predictive marker of COVID-19[43]. ACE2 protein exists in two forms, membrane-bound and circulating (soluble) form. Circulating ACE2 (with an intact N-terminal peptidase domain) is generated by catalytic activity of metalloprotease ADAM17 and released into the extracellular circulation system[44]. Moreover, TMPRSS2 is a type II transmembrane serine protease which competes with ADAM17 for releasing circulating ACE2. As a part of catalytic similarity, both ADAM17 and TMPRSS2 cleave short C-terminal fragment from ACE2. Presence of arginine and lysine residues within 652 to 659 amino acids are required for ADAM17 mediated ACE2 release. Whereas same residues within 697 to 716 amino acids are essential for TMPRSS2 mediating shedding of ACE2. Of note, only cleavage by TMPRSS2 leads to augmented SARS-CoV cell entry, however, ADAM17 activity is not required for SARS-CoV cell entry through fusion[45]. Circulating ACE2 may competitively bind with SARS-CoV-2 and may neutralize the virus, may rescue cellular ACE2 functions which negatively regulate the renin-angiotensin system and slow down the viral entry and spread into cells and protect from lung injury. Due to these protective functions, the soluble form of ACE2 has got therapeutic significance for inhibition of SARS-CoV-2[46]. Contrary to this, circulating ACE2 are increased in patients with hypertension, heart failure, type 1 or type 2 diabetes (DT2) and chronic kidney diseases. The possible reason for elevated levels of ACE2 in these human ailments might be associated with defensive response to circumvent the AngI mediated adverse effects[43]. The above description clearly indicates the significance of ACE2 expression levels in lungs, heart, and vascular cells in diabetes subjects and also highlights its importance as biomarker of morbidity and mortality in COVID-19 patients. In general, it is observed that the children are less susceptible to COVID-19 disease as compared to adults[47]. The possible reason can be attributed with the expression levels of ACE2, but until now, there is no evidence of downregulation of ACE2 or function in children. Perhaps, the possible answer lies in the dynamics of innate immunity of children, fewer comorbidities, differential expression pattern and maturation of viral receptors and perhaps the exposure to one or other members of coronaviruses. Of note, children's immune system produces natural antibodies rapidly with a broader reactivity against common pathogens occurring in the environment[48]. Evolution has bestowed a survival advantage to kids towards combating broad range of known and unknown pathogens.

Evolving Thrombotic Complication in COVID-19: 'Storm of Blood Clots' and Tailoring New Line of Treatment?

Another important evolving pathophysiological observation is the newly identified incidence of thrombotic complications in the critically ill COVID-19 patients. The clinical reports are consistently accumulating linking the thrombotic

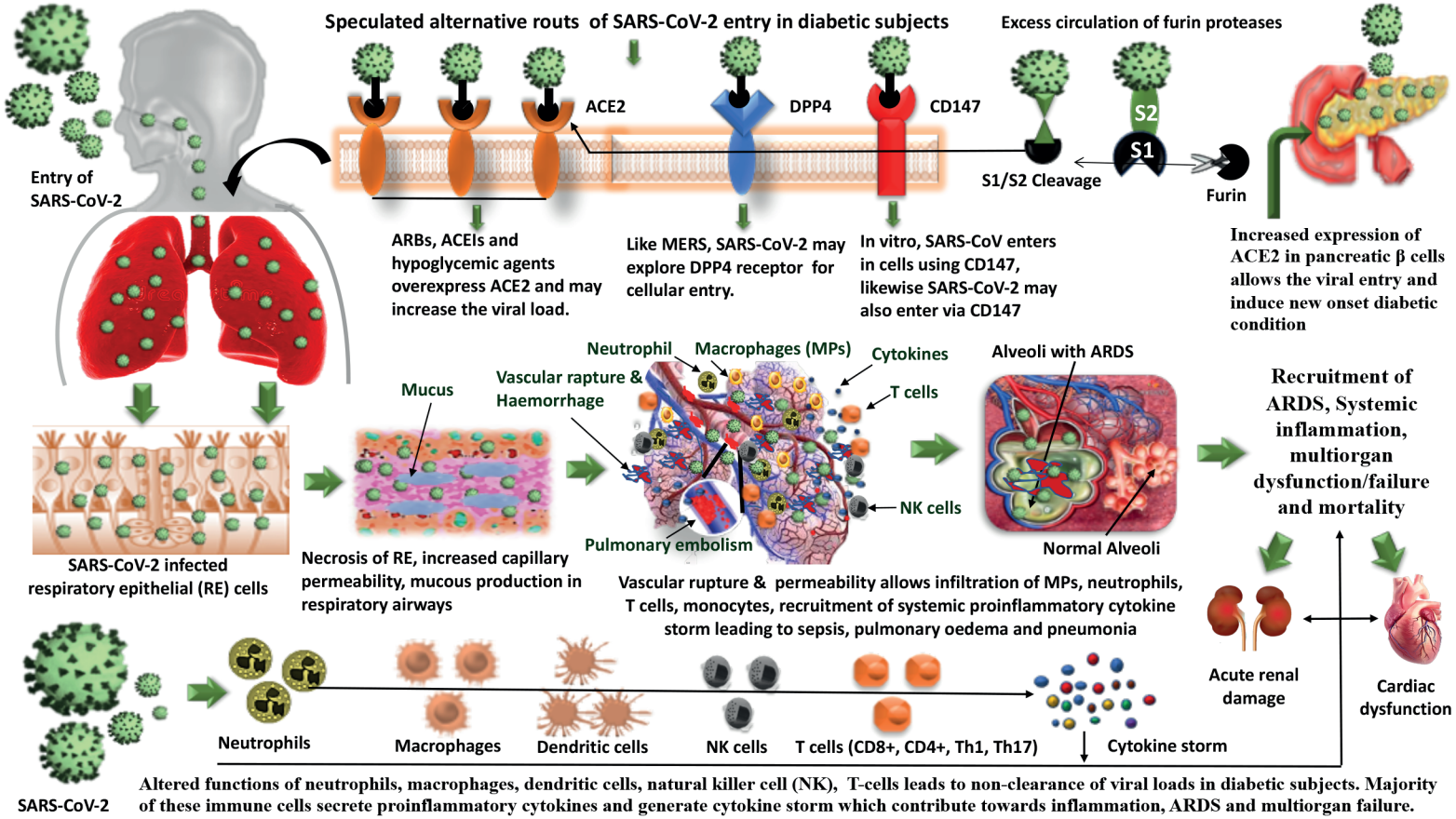

Figure 1. Possible speculative mechanisms of alternative routes (furin induced elevated ACE2, DPP4 and CD147) for entry of SARS-CoV-2 in diabetic subjects causing aggressive ARDS and onset of diabetic condition owing to increased ACE expression in pancreatic B cells. Alternatively, SARS-CoV-2 infection also activates immune cells (macrophages, T cells, NK cells and dendritic cells) leading to secretion of proinflammatory cytokines (cytokine storm) which ultimately recruits systemic inflammation, ARDS, pulmonary embolism, vascular rupture leading to multiorgan dysfunction and mortality. SARS-CoV-2 infected RE cells undergoes necrosis leading to generation of mucous which contributes towards causation of aggressive ARDS.

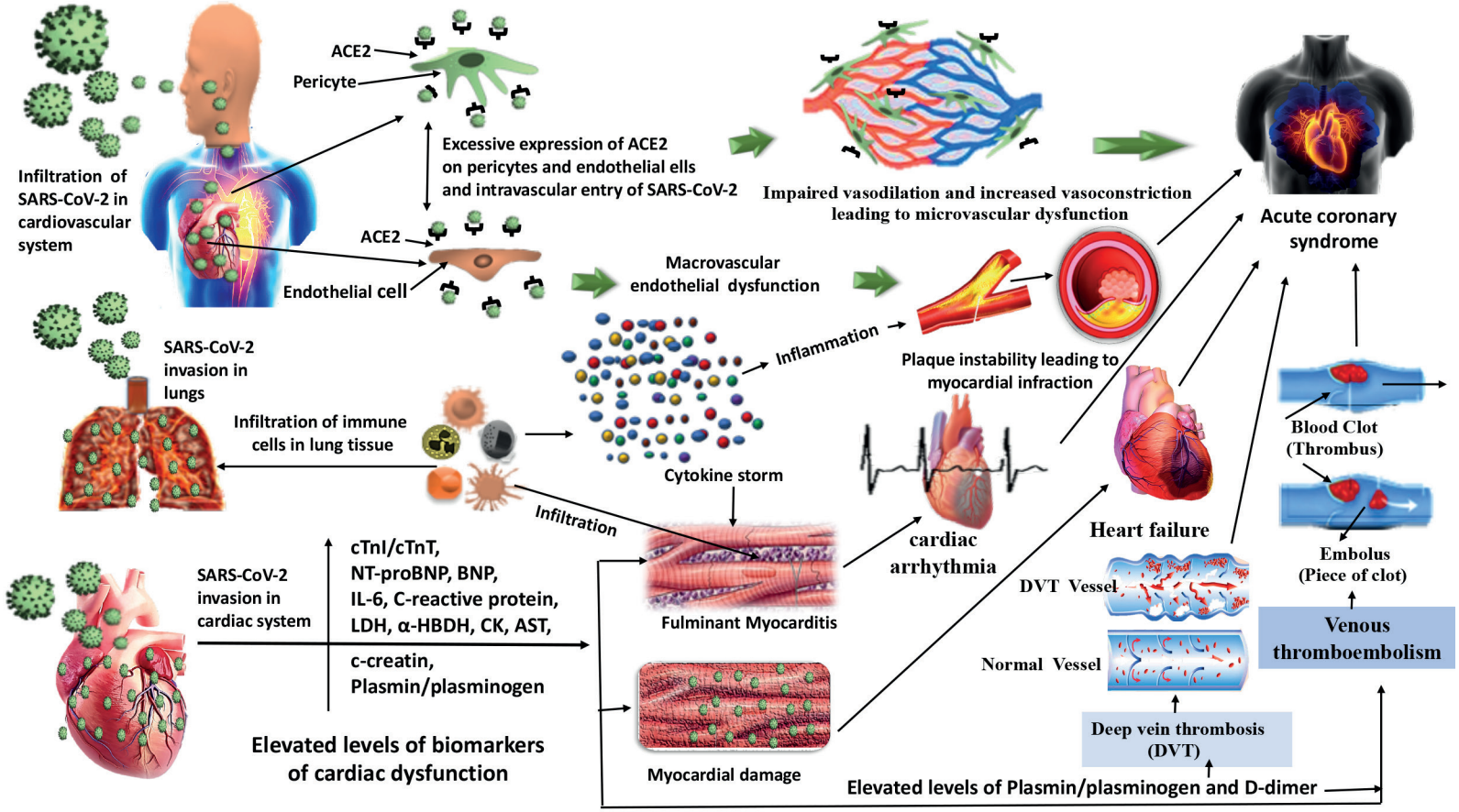

Figure 2. Pathophysiology of cardiovascular dysfunction in COVID-19: Speculative mechanisms and key manifestations in acute coronary syndrome. Increased expression of ACE2 in endothelial cells and pericytes infiltrates the SARS-CoV-2 in cardiovascular system causing microvascular and macrovasular dysfunction (impaired vasodilation and increased vasoconstriction). SARS-CoV-2 infection is associated with progressive systemic inflammation and immune cell hyperactivation leading to generation of proinflammatory 'cytokine storm'. The hyperactivated immune cells (neutrophils, T cells, macrophages, monocytes and dendritic cells) also infiltrates into cardiac muscular system and causes myocarditis and myocardial damage leading to cardiac arrhythmia and heart failure. The proinflammatory cytokines also contributes towards instability of atherosclerotic plaque which may cause myocardial infraction. In COVID-19 disease progression the biomarkers cardiac disfunctions such as cTnI/cTnT, NT-proBNP, BNP, IL-6, C-reactive protein, LDH, α-HBDH, CK, AST are elevated mostly in critically ill COVID-19 patients. The thrombotic complications like deep vain thrombosis (DVT) and venous thromboembolism are associated with increased levels of plasmin/plasminogen. The series of SARS-CoV-2 induced cardiovascular and cardio muscular dysfunctions ultimately leads to acute coronary syndrome

complications, such as pulmonary embolism (PE), deep-vein thrombosis, myocardial infarction or systemic arterial embolism, ischemic stroke etc. with ICU admitted critical COVID-19 patients (Figure 2). Amongst the few initial reports, the venous and arterial thromboembolic complications in COVID-19 patients were reported from the academic hospital in Milan, Italy[10]. Over 31% incidences of thrombotic complications were observed in ICU admitted COVID-19 patients from Laeiden, Netherlands[49]. In Wuhan, China, the cradle of COVID-19, the clinical analysis of 143 hospitalized COVID-19 patients revealed that, 46.1% patients developed lower extremity deep vein thrombosis (DVT), 34.8% were observed with proximal DVT and 65.2% were diagnosed with distal DVT. Moreover, higher cardiac injury, lower oxygenation index, worse prognosis and higher mortality was associated with DVT patients as compared to patients with no DVT[50]. Another report[51] from a single center ICU in China reported 25% venous thromboembolism (VTE) incidence from a cohort study of 81 ICU admitted COVID-19 patients. In a French multicenter ICU cohort study of 150 COVID-19 patients, over 43% patients demonstrated prevalence of thrombosis; ironically the thrombotic clinical manifestations were also prevalent in patients who were treated with prophylactic or therapeutic anticoagulation therapy[52]. Data of 79 patients admitted to critical care in Guy's and St Thomas' NHS Foundation Trust, London, UK, clearly showed that over 15% patients were diagnosed with at least one episode of image-proven thromboembolism[53]. Interestingly, the D-dimer (predictive marker of thrombosis) levels were significantly higher in critically ill COVID-19 patients who demonstrated thrombotic complications. The higher levels of D-dimer can also be attributed with inflammatory and procoagulant state of COVID-19[10,50,53-55]. The worldwide incidence of emerging thrombotic complications in COVID-19 patients also inspired the physicians for testing the effect of anti-coagulant, anti-inflammatory and antibiotic treatment for mitigating the risks of thrombotic complications mostly in ICU admitted COVID-19 patients and also a prophylactic measure for management of COVID-19.

As a part of management of thrombosis, International Society on Thrombosis and Hemostasis (ISTH) and American Society for Hematology have recommended that all hospitalized COVID-19 patients (excluding active bleeding and platelet count $<25x10^9/l$) should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation drugs, such as low molecular weight heparin (LMWH) or fondaparinux[56,57]. Although coagulopathy has been linked with mortality of COVID-19 patients, and intervention of anticoagulant drugs especially LMWH, are known to reduce the mortality in COVID-19 patients with coagulopathy[58], however, the puzzle of implementing anticoagulant therapy is still uncertain due to the lack of clinical trial evidence and some controversial reports which describe that ICU patients treated with a therapeutic dose of LMWH developed thrombosis besides giving this escalated dose. The report also described that a cumulative incidence for VTE was also observed in over 56% in those patients[59]. In a cohort study of 69 ICU admitted COVID-19 patients, a clear evidence of heparin resistance has been reported. The outcome of the study showed that heparin resistant was observed in patients who received anticoagulation therapy with unfractionated heparin and LMWH. Almost similar type of heparin resistance was observed in another clinical setting[60,61]. Moreover, the COVID-19 patients who are already on the episodes of anti-coagulation or anti-platelet therapy are also associated with aggravated bleeding risk[62]. Nevertheless, the patients also need to be counseled for avoiding pro-thrombotic supplements, such as vitamin K or E and medications, such as selective cyclo-oxygenase-2.

D-dimer as a Predictive Marker of Thrombotic Complication in COVID-19

After a thrombus or clot has formed, attained stability and achieved its hemostatic function, it is normally degraded by employing a fibrinolytic system which results into resuming the impaired blood supply. The process of fibrinolysis typically initiates by converting plasminogen to plasmin by a plasminogen activator, mostly on the surface of fibrin surface, and then plasmin mediated degradation of fibrin takes place in a systematic manner resulting into formation of fibrin degradation products (FDPs). Multiple structurally diverse FDPs, such as fibrinopeptide B, fibrin degradation monomers and dimers are generated. During the cleavage of fibrin polymers by plasmin at the D fragment site, there is generation of a smallest cross-linked D-dimer comprising of two D regions of the adjacent fibrin molecules connected by a γ-γ bond[63]. The level of the D-dimer fragment generated is associated with the degree of thrombosis and plasmin activity (Figure 2). D-di-

mer levels have been frequently used as predictive and prognostic markers in number of thrombotic disease conditions such as deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation and cancer-related thrombotic states[64,65] (Figure 2). D-dimer values are widely used by the clinicians as a surrogate marker for fibrinolysis and is usually elevated in thrombotic conditions. D-dimer levels might help in early diagnosis of these high-risk thrombotic comorbidities and also predict disease prognosis. In general, under normal physiological conditions, the D-dimer values normally ranges from 0.0-0.5 μg/ml and values >1 μg/mL are associated with higher risk of thrombosis related mortality[66].

Series of studies[10,14,26,50,53-55,67-69] have demonstrated the elevated levels of D-dimers predominantly detected in patients with severe COVID-19. Multivariate regression analysis further suggested that D-dimer levels (<1 mg/L) is a prominent risk factor for mortality and significant poor prognostic factor in COVID-19 patients[10,14,26,50,53-55,67-69], however, the clinical relevance of D-dimer in COVID-19 patients is poorly understood. Increased levels of D-dimer more than 1.5 μg/ml were observed in COVID-19 patients; VTE with 850% sensitivity, 88.5% specificity with a negative predictive value of 94.7% and over 40% of such patient died[51]. In a systematic review of pouring 6,892 COVID-19 patients, the meta-analysis of 3,496 patients revealed that the D-dimer levels were high in 34.8% patients and the values were associated with severe clinical course with an odds ratio of 4.03[70].

In a retrospective cohort study comprising of 191 COVID-19 patients, the levels of D-dimer were remarkably >1.0 μg/ml and were associated with increased risk of mortality. Of note, the D-dimer levels of 2.0 μg/ml or above was found to be the optimum cut-off to predict in-hospital mortality of COVID-19 patient[71]. Furthermore, on admission of patients, the D-dimer levels can be conveniently used as a triage for admitting patient in ICU or critical care. The clinical observations also revealed that the median D-dimer levels were higher in ICU patients (2.4 mg/L) as compared to 0.5 mg/l values in non-critical patients[26]. In a cohort study of 343 COVID-19 eligible patients, the optimum D-dimer cutoff value to predict in-hospital mortality was observed to be over 2.0 μg/ml (four-fold increase *vs.* normal) with a sensitivity of 92.3% and a specificity of 83.3%. Patients with D-dimer levels ≥2.0 μg/ml had a higher incidence of mortality as compared to those patients who had D-dimer levels less than 2.0 μg/ml[71]. In summary, measuring D-dimer levels have been recommended for COVID-19 patients, but its optimal cutoff levels remain to be precisely defined. In general, fourfold increase in D-dimer (≥2.0 μg/ml) levels on hospital admission can be considered as an optimum cutoff to predict in-hospital mortality of COVID-19 patients. Due to the diagnostic and prognostic significance of D-dimer levels in thrombotic state and its evolving correlation with mortality, estimating the levels of D-dimer along with routine tests might help physicians in tailoring optimum treatment modality for effective management of COVID-19 patients.

Linking the Levels of Plasminogen/Plasmin in Comorbid Diseases of COVID-19: The Gamble of Risk and Benefits of Fibrinolysis in COVID-19

In a classical process of thrombosis, the activated platelets (in response to vascular injury) provide series of signaling cues leading to activation of thrombin from its zymogen prothrombin. Active thrombin further polymerizes fibrin by cleaving it into small peptides, and thus, converts soluble fibrinogen into insoluble fibrin and forms a clot or "thrombus" incorporating the circulating red blood cells, white blood cells, and platelets. After healing of the injured blood vessel, the effete thrombus is subjected for plasmin mediated lysis. The plasminogen activator system is a broad-spectrum protease system where plasmin is generated from plasminogen (zymogen) on cell surfaces or on the surface of the fibrin clot either by tissue plasminogen activator or urokinase[72].

The elevated levels of D-dimer, FDPs, prothrombin time prolongation and uniquely increased fibrinogen levels clearly indicates that the progression of COVID-19 is associated with hyperfibrinolysis[10,50,53-55]. Also, plasminogen levels are elevated in COVID-19 patients, perhaps this could be a possible mechanism for enhanced susceptibility to SARS-CoV-2 infection and related morality in patients having history of pre-existing comorbidities[69] (Figure 2). The most important considerations of plasminogen/plasmin system in pathogenesis of COVID-19 that needs to be considered is the role of plasmin in the cleavage of S-protein of coronaviruses. As like other proteases, such as TMPRSS family members, elastase, trypsin, cathepsins, the S protein of coronaviruses may also be cleaved by plasmin, as it has demonstrated the cleavage of the S proteins of SARS-CoV under *in vitro* settings. Cleavage of S protein may facilitate its binding with ACE2 and

thereby enhance the SARS-CoV-2 entry into the host cells[73]. This role of plasmin which enhances the virulence and infectivity of SARS-CoV-2 can be considered as a target for developing plasminogen/plasmin specific anti-protease agents against COVID-19.

In fact, coagulopathy originates from concomitant activation of coagulation and fibrinolysis with a prominent role played by proinflammatory cytokines (cytokine storm), the viral sepsis causing depletion of coagulation factors and decreased platelet count leads to thrombohemorrhage. The plasminogen mediated fibrinolysis in tissues and organs leading to excess generation of D-dimer, FDP, and reduction in platelet count also contributes towards risk of bleeding[69]. The elevated level of plasminogen is a common clinical feature in COVID-19 severity related chronic diseases like hypertension, CVD, diabetes and chronic renal disorders. More precisely, the elevated levels of plasminogen/plasmin aggravate the cleavage of epithelial sodium channel (ENaC) subunits, situated at the apical membranes of epithelial cells in the lung, airway and kidney. This cleavage of ENaC facilitates the entry of Na^+ ions into epithelial cells leading to increase in hypertension (Figure 2). In fact, the Amiloride is a tailored drug which specifically attenuates the urine plasminogen activation and thereby lowers blood pressure[74].

Cardiovascular comorbidities are one of the most important factors attributed with severity of COVID-19 and the human subjects with coronary artery disease has been reported 1.7-fold higher levels of plasmin as compared to healthy humans, which perhaps may contribute towards cardiovascular injury. In general, remarkably elevated levels of plasmin and urinary plasminogen are estimated in patients with chronic heart failure[75] (Figure 2). Also, in diabetic conditions (type I and II), higher levels of plasminogen have been documented in hypertensive diabetic patients. Aberrant plasmin levels in pre-urine might abnormally activate the ENaC in type II patients and induce microalbuminuria causing damage to the glomerular filtration efficiency of the kidney[76]. In a clinical observation, it was observed that over 49% of COVID-19 patients developed acute respiratory distress syndrome (ARDS) as compared 9% patients who were devoid of ARDS[77]. Significantly higher levels of cleaved plasmin and plasminogen have been reported in the bronchoalveolar lavage fluid of ARDS patients[78]. Due to the important role of plasminogen/plasmin system in tissue/organ injury, it is recommended that the normalization of hyperfibrinolysis may be a therapeutic modality in the management of COVID-19.

In a conventional clinical practice, targeting the fibrinolytic and coagulation system has been considered as a basic prerequisite for improving the therapeutic efficacy of ARDS treatment[79]. As a matter of previous state-of-the-art, the administration of plasminogen activators is known for reducing the ARDS progression and ARDS induced deaths in animal model studies and also in phase I human clinical trial[80]. A recent clinical investigation counteracting the adverse effects of plasminogen induced hyperfibrinolysis, its protective effects have been reported in COVID-19 patients. It was observed that inhalation of freeze-dried plasminogen therapy dramatically improved the lung lesions and hypoxemia in clinically moderate patients, improved oxygen saturation in clinically severe & critical patients and improved heart rates in all grade COVID-19 patients[81]. The outcome of this study indicates that the elevated plasminogen levels can be an independent factor in stratifying the risk (bleeding) or benefits to COVID-19 patients and inspires to conduct further research in defining the dose, route of administration and duration of treatment. Currently there is no clinical trial data available which describe the efficacy of fibrinolytic therapy in COVID-19, but there is equal opportunity to explore the therapeutic usage of t-PA, urokinase or plasmin in clinically complicated COVID-19 patients with ARDS[82]. The outcome of a phase II clinical trial (NCT 04357730) investigating the effect of fibrinolytic therapy to treat ARDS in COVID-19 settings is awaited.

Hypertension and the Puzzle of Prescribing ARBs and ACEI Drugs in COVID-19 Management?

The worldwide clinical observations have linked the hypertension as the most commonly observed comorbidity in relation to COVID-19 morbidity and mortality[3,14,18]. In the present state-of-the-art, the mechanistic significance of blood pressure as a risk factor for COVID-19 is poorly understood. As such blood pressure has no relevance with susceptibility towards the SARS-CoV-2 viral infection, however, it is believed that stable blood pressure is essential for management of variety of human ailments including COVID-19. In a pooled analysis study, it was estimated that, the hypertension increases the risk of COVID-19 severity and mortality by nearly 2.5-fold[3].

As a part of symptomatic supportive treatment, physicians usually prescribe the angiotensin receptor blockers (ARBs) and an ACE inhibitor (ACEI) to COVID-19 patients to drop down the hypertension and ameliorate the cardiovascular disorders. The preclinical data demonstrated that the treatment of ARBs and ACEI could upregulate the ACE2 expression in cardiovascular and renal systems[83,84], as ACE2 happens to be a key receptor for cellular entry of SARS-CoV-2, the concerns have been raised with an assumption that ARBs and ACEIs would increase the susceptibility for SARS-CoV-2 infection and augment the severity of COVID-19 in hypertensive and CVD patients treated with these drugs[85] (Figure 1).

Before assessing the feasibility of extrapolating these circumstances in human subjects, some preclinical and clinical investigations need to be revisited for example, ARBs have demonstrated potential benefits in providing protection to lung injury induced by COVID-19[86]. In the preclinical myocardial infarction animal model studies administration of ramipril, valsartan or their combination have no effect on expression of cardiac ACE2[87]. No clinical data are available explaining the effects of ARBs and ACEIs on expression of ACE2 in human subjects. Also, most importantly, the clinical data showing the effects of ARBs and ACEIs on expression of lung ACE2 are not available either in animal models or in humans. There is no preclinical or clinical evidence describing the role of ARB induced ACE2 levels in facilitating the entry of SARS-CoV. Of note, the doses of ARBs and ACEIs utilized in different animal model studies were much higher than the doses usually used in clinical practice, therefore the apparent effects of these drugs on regulation of ACE2 expression may not mimic the clinical situations in human subject[88].

ACEIs and ARBs have demonstrated effects in ameliorating ARDS, myocarditis and acute kidney injury (elevated levels of urea and creatine), which are observed in COVID-19 patients. Due to these benefits, ARBs have been recommended as a treatment modality for management of COVID-19 and related complications[89]. The outcome of a single-center retrospective analysis study enrolling 112 COVID-19 patients revealed that the use of ARBs and ACEIs apparently did not demonstrated any impact on the morbidity and mortality of COVID-19-19 patients with CVD[90]. An Italian-based clinical trial (NCT04318418) investigating the effects of ACEIs and ARBs on the severity of COVID-19 is in progress (Clinicaltrials.gov). So, considering the circumstantial literature, it seems that there is no clinical evidence which relates the effect of ACEIs or ARBs in augmenting the susceptibility and severity of COVID-19. Therefore, according to the guidelines of European Society of Cardiology, European Society of Hypertension, American Heart Association, Heart Failure Society of America and American College of Cardiology; in the present situation the clinical usage ARBs and AECIs should not be discouraged in the mainstream of well-established standard integrated therapeutic approaches for the management of high-risk COVID-19 patients with heart failure, prior myocardial infarction, CVD, cerebrovascular disease and also for the patients with stable hypertension[91,92].

Risk of Cardiovascular Complications in COVID-19

In a meta-analysis comprising 46,248 COVID-19 patients from 8 different clinical studies, CVD was investigated as the third most prevalent comorbidity in COVID-19 patients (5%, 95% CI 4%-7%). Of note, the patients with severe illness had a greater risk of CVD (OR 3.42, 95% CI 1.88-6.22). Perhaps the foremost well-established major upcoming concern of CVDs in relation to COVID-19 morbidity and mortality is the association of increased risk of disease severity and mortality with pre-existing CVD. Moreover, the SARS-CoV-2 infection is also associated with series of direct and indirect cardiovascular complications, such as arrhythmias, acute myocardial injury, myocarditis, stress-cardiomyopathy, cardiogenic shock and venous thromboembolism[93] (Figure 2). Nevertheless, the current supportive therapeutic regimes of COVID-19 can adversely affect the cardiovascular system owing to their side effects[94]. In general, series of cardiac complications are commonly observed in patients with pneumonia. Of note, the SARS-CoV-2 virus is known for causing ARDS and severe pneumonia. Reports from several countries have made it clear that the patients of COVID-19 with cardiovascular comorbidities have higher mortality risk. Overall, myocardial injury is the most commonly observed cardiac complication in COVID-19 responsible for worse prognosis[93].

While describing the ACE2 linked cardiovascular damage, the single-cell RNA sequencing data have showed that over 7.5% of myocardial cells have positive ACE2 expression and thereby mediate SARS-CoV-2 entry into cardiomyocytes

and may cause cardiotoxicity[95]. However, the previous reports[96] describe that relationship between ACE2 expression and SARS-CoV-2 virulence is not uncertain, as once the SARS-CoV-2 enters in the host cell it subsequently downregulates the expression of ACE2, and this function has been described as a vital regulatory mechanism for maintaining the cardiac function. Therefore, the theoretical speculations about the ACE2 mediated increased risk of SARS-CoV-2 infection and its role in cardioprotection is yet to be investigated in human subjects[86]. The clinical analysis of 68 fatal COVID-19 cases from Wuhan, China showed that 36 patients (53%) died of respiratory failure, 5 (7%) cases with myocardial injury died due to circulatory failure, and 22 patients (33%) died from both complications[2]. Molecular mechanisms of myocardial injury in relation to COVID-19 remain unknown. Another report from Wuhan China considering 138 in patients with COVID-19, in ICU patients the levels of biomarkers of myocardial injury were significantly high as compared to non-ICU care[68]. Number of studies have reported that cardiac comorbidities most notably fulminant myocarditis are potential outcomes associated with of SARS-CoV-2 infection. In a recent clinical observation[14] from hospitalized Chinese COVID-19 patients, over 23% heart failure cases have been reported. Of note, 52% of non-survivors succumb to death because of heart failure as compared with 12% of survivors. The molecular underpinnings of cardiovascular injury are poorly understood in COVID-19. Different mechanisms are postulated while linking the COVID-19 with morality for example, one theory suggests that COVID-19 may aggravate pre-existing CVD and cardiovascular risk factors and may increase the susceptibility for the development of new cardiovascular comorbidities. Alternatively, another opinion suggests that CVD or myocardial injury may predispose to poor prognosis in COVID-19 patients, which is reported by several studies[97,98] describing that established that CVD increases the severity of COVID-19 thereby leading to higher morbidity and mortality.

The current used drugs for the treatment of COVID-19 are associated with cardiovascular side effects and toxicities. Of note, the data for these side effects and toxicities are related with patients who are using these drugs chronically, for example the use of Chloroquine, or Hydroxychloroquine and Rocilizumab for the management of autoimmune diseases, Ribavarin and IFN-a for treatment of hepatitis, and Lopinivir or Ritonivir for management of HIV infection. Thus, short-term use toxicities and side effects of these drugs is not clear. For example, Remdesivir is a trial drug used in the treatment of Ebola, but its cardiovascular side effects and toxicities are not known. The case of antimalarial drugs like chloroquine and hydroxychloroquine which has recently received renewed interest for the prophylactic treatment of COVID-19 was similar, but the clinical data in support of these drugs is poor, while cardiac toxicities are significant. The ventricular hypertrophy, hypokinesia, heart failure, pulmonary arterial hypertension and valvular dysfunction are some of the cardiac side effects and toxicities of the aforesaid drugs, therefore, caution and in-depth clinical investigations are required while prescribing these drugs for the management of COVID-19[99].

It is well established fact that virus induced hyper-inflammation is closely associated with excess release of proinflammatory cytokine and chemokines such as IL-1β, IL-6, IL-8, interferon-gamma and TNF-α, leading to cardiovascular inflammation, unstable plaque formation, myocardial inflammation, thrombotic state, and suppression of myocardial functions[100]. The evolving evidence indicates that patients with severe COVID-19 are reported to develop so called 'cytokine storm' with elevated plasma levels of IL-1β, IL-6, IL-8, TNF-α and ferritin which may aggravate the inflammation related to cardiovascular comorbidities leading to higher mortality rates[101]. Other consequences of SARS-CoV-2 infection includes sepsis and disseminated intravascular coagulation (DIC) which also contribute for cardiac injury. DIC, a marker of severe sepsis, is a life-threatening complication reported in over 71.4% (15/21) of non-survivors *vs.* 0.6% (1/162) of survivors with COVID-19[54]. The clinical observations from Washington State reported the incidence of 33% (7/21) acute heart failure in severe ill patients of COVID-19 even without a past history of mid-left ventricular systolic dysfunction[102]. Also, COVID-19 patients with mild or even absent of respiratory symptoms can also develop cardiomyopathy[103]. Perhaps, the first presentation of COVID-19 is arrhythmia and/or progressive arrhythmia that can be linked with cardiac involvement. The incidence of arrhythmias is most frequently observed in ICU COVID-19 patients (44.4%) as compared to non-ICU (6.9%) patients[68].

The elevated hyperfibrinolysis, active resurgence of inflammation, and incidence of DIC

are observed in immobilized COVID-19 patients in hospitals which might be associated with increased risk of VTE.

As discussed previously, the prevalence of deep venous thrombosis is associated with significant higher level of D-dimer, FDPs and fibrinogen in COVID-19 patients as compared to their normal counterpart[10,50,53-55]. The evidence suggests that a common activation of coagulation system is closely associated with poor prognosis and death of COVID-19 patients.

Biomarkers of Cardiovascular Comorbidities in COVID-19

While grading the severity of COVID-19, expression levels of several cardiac prognostic and diagnostic biomarkers are correlated with cardiovascular complications and related morality. In the current state-of-the-art, series of laboratory biomarkers, such as Cardiac troponin I and T (cTnI and cTnT), D-dimer, Brain Natriuretic Peptide (BNP), Myoglobin (Mb), C-reactive protein, N-terminal-prohormone B-type Natriuretic Peptide (NT-proBNP), Creatinine Kinase-Myocardial Band (CK-MB), Creatinine Kinase (CK), Procalcitonin, Lactose Dehydrogenase (LDH), Mid regional pro-atrial natriuretic peptide (MR-proANP), Mid regional proadrenomedullin (MR-proADM), IL-6, ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hydroxybutyrate dehydrogenase (α-HBDH), c-creatin etc. related to myocardial injury, heart failure, cardiac inflammation are investigated in the COVID-19 patients across the world (Figure 2). With variation in the levels of these biomarkers, the overall trend of levels is elevated in several grades of COVID-19 patients. Of note, the elevated levels of cardiac dysfunction biomarkers were mostly associated with ICU admitted or severe ill COVID-19 patients[39,98,99,103-105].

Of the series of biomarkers described for cardiac health, the most extensively employed biomarker in COVID-19 is the cTnI and cTnT. The sarcomere (a fundamental contractile unit of heart) is made up of thick myosin filament and thin filament comprising of two filamentous actins (F-actin; a polymer of globular actin). The grooves of the F-actin helix are filled with tropomyosin, where troponin is attached. Troponin proteins are made of three functional subunits, i.e., (encoded by different genes) mainly expressed in skeleton and cardiac muscles. Of the three troponin isoforms, such as TnI ('I' for inhibitory activity against actomyosin ATPase), TnT ('T' for tropomyosin bound) and TnC ('C' for Calcium binding), TnI and TnT are mostly used as markers of myocardial infarction or injury. After the onset of myocardial ischemia, the necrotic death of myocytes takes place within 15 minutes. The cardiac troponin (cTn) especially the cTnI and cTnT are released free in venous circulation in the form of ternary and binary complexes[106].

As a valid prognostic biomarker, the levels of cTnI and cTnT are considered as gold-standard for assessing the extent of necrotic myocardial and ischaemic injury irrespective of its cause. In general, the higher levels of cTnI/cTnT are correlated with acute myocardial injury, need for ICU admission, in-hospital death and severe inflammatory state. In a meta-analysis of 341 COVID-19 patients, significantly higher levels of cTnI have been recorded with mean difference (25.6 ng/L, 95% CI 6.8-44.5 ng/L) in patients with critical symptoms as compared to patients with non-severe COVID-19 patient[107]. In a cohort of 416 COVID-19 patient, 82 (19.7%) COVID-19 patients were presented with myocardial injury having significantly elevated levels of serum cTnI[39]. Guo et al[105] observed higher levels of cTnT in 27.8% (52/187) hospitalised COVID-19 patients which developed myocardial injury. The mortality was higher (59.6%) in those 52 patients as compared to 8.9% COVID-19 patients having normal serum cTnT levels. Of note, the COVID-19 patients with elevated cTnT levels and pre-existing CVD had a mortality rate of 69.4%. Moreover, patients with raised serum cTnT levels but no history of established CVD still had relatively higher rates of mortality (37.5%). The data show the prognostic significance of measuring elevated levels of cTnT in all COVID-19 patients which are not linked with presence of pre-existing CVD. On the other hand, patients with normal serum cTnT levels but having history of CVD had significantly much lower mortality rate (13.3%) as compared to morality rate of 59.6% in patients with increased levels of cTnT[105].

BNP is a 32-aa peptide synthesized mostly by the ventricles and in brain as well. Proteolytic cleavage of pro-BNP (108 aa) results in formation of BNP and NT-pro-BNP (76 aa). Both, BNP and NT-pro-BNP have been considered as a sensitive diagnostic biomarker for heart failure and myocardial injury. The levels of BNP and NT-pro-BNP are the markers of adverse outcomes after the acute myocardial injury[108]. Guo et al[105] reported that the raised levels of cTnT were associated with increased levels of serum BNP ($p < 0.001$).

Of note, the gradual and progressive elevation of serum cTnT and BNP levels were associated with health deterioration as compared to low and stable levels of serum BNP in successfully discharged COVID-19 patients. In a single center cohort study[39] from Wuhan China, it was observed that the COVID-19 patients having established cardiovascular comorbidities, the levels of NT-proBNP were found greater than 900 pg/ml *vs*. normal levels of <125 pg/ml. Basically, increased myocardial wall stress happens to be a key factor for excess secretion of a heart failure marker NT-proBNP and its levels are also associated with acute renal injury and proinflammatory signalling molecules. A report[105] has demonstrated that the elevated levels of NT-proBNP are significantly correlated with morality of hospitalized COVID-19 patients. The outcome of a recent clinical trial (NCT04292964) showed that 88.64 pg/ml was found to be the best cut-off value of NT-proBNP for predicting in-hospital death of COVID-19 patients. However, after adjustment of the data with potential risk factors, the study suggested that the cut off value of NT-proBNP (88.64 pg/ml) in COVID-19 patients was far lower than the threshold value to diagnose heart failure (450 pg/mL for < 50 years or 900 pg/mL for 50-75 years), and therefore, the prognostic significance of plasma NT-proBNP in critical COVID-19 patients may not be fully ascribed to heart failure either induced by the virus or hypoxic state. The levels of NT-pro BNP in critical patients might be an independent risk factor for in-hospital mortality of COVID-19 patients[109].

Collectively, the accumulated evidence linking the coagulation related morality in COVID-19 patients clearly indicates the significance of D-dimer as predictive biomarker of morbidity and mortality in both ICU and in-hospital admitted COVID-19 patients. The increased levels of D-dimer and its correlation with coronary thrombosis in COVID-19 patients has been previously described[10,50,53-55]. The biomarkers, such as LDH, α-HBDH, CK and AST, are cardiac enzyme biomarkers and their elevated levels may not categorically represent the myocardial injury, perhaps the increased levels may be associated with damage to the lungs, kidneys, liver, or other organs. It is well established that LDH levels are significantly increased in thrombotic microangiopathy which is closely associated with renal damage and myocardial injury. In a clinical observation focused on 99 COVID-19 patients, over 13 % patients showed significant increase in levels of CK and over 76% patients showed raised levels of LDH[7]. Moreover, Guan et al[110] reported that over 13.7% of COVID-19 patients had higher levels of CK and over 37.2% patient showed increased levels of LDH. In a systematic review of literature[111] considering 4189 COVID-19 patients from 28 studies, elevated higher mean troponin, CK-MB, myoglobin, and NT-proBNP were attributed with higher mortality of COVID-19 patients. The main significance and advantage of considering myoglobin as a cardiac biomarker is its immediate release from the damaged cells than other cardiac markers, allowing the early diagnosis of acute myocardial injury. The raised levels of high-sensitivity cTnT, IL-6 and serum ferritin (basically inflammatory biomarkers) were reported in COVID-19 non survivors having higher rates of heart failure (52% *vs*.12%) and acute cardiac injury (59% *vs*. 1%) as compared to survivors[14].

Different biomarkers of cardiac health are investigated in various grades of COVID-19 patients, however considering the prognostic potential of cardiac biomarkers, it is important to probe whether the increased levels are associated with poor prognosis of COVID-19 or simply they are the consequence of disease progression. Moreover, the underlying mechanisms in relation to increased levels of abnormal biomarker, for example several biomarkers of thrombosis, are elevated in hepatic or inflammatory diseases and therefore are nonspecific. Further molecular studies investigating the role of these biomarkers may allow the better insight into the pathophysiology of COVID-19.

Alarm: Diabetes Patients Should Be More Cautious and Alert Towards COVID-19

Since the scientific community started investigating the impact of pre-existing comorbidities on morality of COVID-19 patients, series of clinical reports have described the strong association of diabetes with almost two-fold increase in mortality and severity of COVID-19, as compared to non-diabetic human subjects[6,33,112]. In the current state-of-the-art, the molecular mechanisms of diabetes induced disease severity and mortality of COVID-19 is not clear. As discussed previously, the higher expression of ACE2 in various organs has been demonstrated in diabetic rodent animals[29,30,33]. In diabetic patients the expression of ACE2 varies with disease progression, for example in early phase of the disease, the ACE2 expression is elevated. Perhaps the increased expression of ACE2 is for counteracting the over activity of ACE and minimizing the damage. But

in the later phases of diabetic progression ACE2 is downregulated. It has been also reported that reduced levels of ACE2 are associated with diabetic nephropathy, increased oxidative stress in the pancreas, decreased glucose tolerance, and altered insulin secretion. Therefore, in diabetic state there is a need to induce upregulation of ACE2 for restoring the positive effects of ACE2. For this achievement, several drugs especially ARBs and ACEIs have been tailored with the end effect of increasing the levels of ACE2[31]. It is speculated that ARBs and ACEIs might upregulate the ACE2 levels thereby increase the susceptibility for SARS-CoV-2 infection and augment the severity of COVID-19[85] (Figure 1), while in chronic hyperglycemic state, the reduced levels of ACE2 may predispose the cells to inflammation and damaging effect of the virus. This explains the "double-edged sword" regulatory mechanism of ACE2 in diabetes and metabolic syndrome.

Moreover, hypoglycemic agents and ACE inhibitors (widely used in DT2 treatment) upregulate the expression of ACE2 and may increase the susceptibility for SARS-CoV-2 infection[29,30,33]. Moreover, increased expression of ACE2 in pancreatic β cells may allow the entry of virus inside the cell and may paralyze the β cell function and induce new onset diabetic condition[35]. It is a general clinical observation that hypertension and diabetes coexist since over 70% of diabetic patients have hypertension. ARBs and ACEI are usually prescribed for management of hypertension in diabetic patients. The preclinical data suggest that administration of ARBs and ACEI could up regulate the ACE2 expression in cardiovascular and renal systems[83,84]. Therefore, hypertension together with diabetes has been observed as leading risk factor for morbidity and mortality in COVID-19[33] (Figure 1).

In general, the proteases are usually upregulated in diabetic subjects. It has been also observed that the circulating levels of furin (a cellular protease) which is involved in cleaving the S1 and S2 domain of spike protein of SARS-CoV-2 and thereby facilitating viral entry in cell, are raised in diabetic patients[113]. These observations may support the hypothesis that patients with diabetes may be more susceptible to SARS-CoV-2 infection. The diabetic state is also associated with overexpression of CD147 blood receptor. CD147 is involved in several metabolic pathways and diseases in general and virus infection in particular[114]. Interestingly, the structure of SARS-CoV-2 spike protein (SP) is almost superimposed with the SP of SARS-CoV[36]. In previous studies[115] it has been demonstrated that CD147 plays a crucial functional role in facilitating the entry of SARS-CoV in host cells. Further, the recent preclinical studies[115] clearly demonstrated the invasion of COVID-19 virus in human host cells via binding of CD147 with SP of SARS-CoV-2. The dipeptidyl peptidase 4 (DPP4) has been identified as prime receptor for Middle East Respiratory Syndrome Coronavirus entry into cell. There are also speculations that DPP4 may facilitate the entry of SARS CoV-2 into the cell (Figure 1). DPP4 inhibitors are frequently used in the treatment of diabetes and it is hypothesized that perhaps the widespread clinical use of DPP4 inhibitors in India and several other countries may be associated with providing protection from infection to individuals with diabetes[116]. These novel routes of SARS-CoV-2 entry might be associated with excessive viral load leading to increased morbidity and mortality of COVID-19 patients. The aforesaid preclinical ACE2 linked findings with diabetes have not been confirmed in human subjects and therefore we have still not understood the pathophysiological mechanisms linking the diabetic state with severity and morality of COVID-19 (Figure 1).

There are few more hypothesis to answer why diabetic state may aggravate the severity of COVID-19. The possible link between diabetes and aggressive progression of COVID-19 morbidity and mortality is also attributed to hemoglobin. In diabetic patients usually the percentage of glycated hemoglobin is more as compared to normal human subject. It is hypothesized that the surface proteins of SARS-CoV-2 may bind with the heme molecule in RBCs and might separate iron from the molecule and forming a porphyrin leading to reduced carrying of oxygen and carbon dioxide, which perhaps recruit cell death and inflammatory processes in the lungs[117]. Hepcidin (a liver-derived peptide hormone), plays a key role in regulation of systemic iron homeostasis. In brief, 'hepcidin is to iron as insulin is to glucose'[118]. Hepcidin allows iron entry in cells by down regulating ferroportin (an iron transporter). It has been speculated[118] that the hepcidin-mimetic action of SARS-CoV-2 might induce internalization or blockage of ferroportin leading to progressive hyperferritinemia and anemia. In a diabetic state hepcidin levels are elevated and increased hyperferritinemia leads to ferroptosis (a kind of programmed cell death) along with generation of high oxidative stress and lipoperoxidation consequently increasing the mitophagy and cell

apoptosis or necrosis[119]. Further, hyperferritinemia may cause several autoimmunity mediated direct and indirect multiple organ injuries by inducing macrophage activation syndrome, coagulopathies, hemochromatosis-like liver injury, and/or other ferroptosis-driven syndromes in diabetes patients[120]. These findings are yet be established in COVID-19 patients.

In general, due to compromised immune functions (mostly innate immunity), diabetic patients have a greater risk of respiratory infections. Even a transient hyperglycemic condition impairs the innate immune response to infections. More precisely, the altered T-cell, macrophages, and natural killer cell functions along with defective complement system leads to non-clearance of viral loads in diabetic subjects[121]. It is well established that diabetic patients usually possess a state of metabolic chronic inflammation that may predispose them to increased release of cytokines. Series of clinical observations have attributed the severity of COVID-19 with the level of dysregulated biomarkers of systemic inflammation[14,31,122]. Perhaps the "Inflammatory axis" link between diabetes patient and COVID-19 may be one of the prominent reasons of aggravating the severity of disease as the elevated levels of pro-inflammatory cytokines (cytokine storm) have been associated with multi-organ failure and severity of COVID-19[123]. In a retrospective single center clinical observational study conducted in China[124], 48 severe COVID-19 patients with diabetes were compared with critically ill 145 COVID-19 patients. It was observed that patients with diabetes had elevated count of white and neutrophil cells, CRP, IL-6, IL-8, IL-2R, D-dimer, NT-proBNP, LDH levels and lower levels of lymphocyte count. These clinical investigations clearly outline the increased status of proinflammatory cytokines in diabetic subjects as compared to non-diabetic but severe COVID-19 patients.

The clinical observations in COVID-19 diabetic patients also revealed that there is significant decrease in population of certain subsets of immune cells, such as CD4+ and CD8+ T cells which are indispensable for manifestation of effective immune response. On the other hand, there is increased proportion of proinflammatory immune cells such as Th17 cells in COVID-19 diabetic patients[33]. Moreover, the interrelationship between ageing and inflammatory processes is well established which also helps in understanding the link between diabetes and severity COVID-19 as both the incidence of diabetes and the severity of COVID-19 are more prevalent in the aged population[125]. It has been demonstrated that the process of ageing and immune dysfunction both are progressively coevolving processes with ageing and are associated with increasing inflammation[126]. Besides the clinical evidence linking the diabetes as an important risk factor for morbidity and mortality in COVID-19, we are still lacking the molecular underpinnings associated with physiological processes making the COVID-19 prognosis worst in diabetic condition.

Dynamics of SARS-CoV-2 Induced Immune Dysfunctions

In general, the factors like ageing, immunosuppression, malnutrition and co-morbid status of health are associated with inability of our immune system for adapting to novel set of immune triggers. As like any viral infections, SARS-CoV-2 also activates the innate and adaptive immune panels. However, the abrupt and uncontrolled innate immune responses and impaired adaptive immune signaling might contribute towards local and systematic tissue damage. More precisely, in severe COVID-19 patient lymphopenia happens to be a common immune signature wherein the number of immune regulatory cells like B cells, $CD8^+$ T, $CD4^+$ T cells, natural killer cells, monocytes, eosinophils and basophils etc. are drastically reduced[28,127,128] (Figure 3). Also, in the bronchoalveolar lavage fluid of critically ill COVID-19 patients, there is occurrence of highly inflammatory phenotype of monocyte originated $CN1^+$ population of macrophages[129]. Moreover, severe COVID-19 patients demonstrated significantly increased number of $CD14^+$ and $CD16^+$ inflammatory monocytes in peripheral blood. Of note, these immune cells are known to secrete inflammatory cytokines, such as IP-10, MCP1 and MIP1α/CCL3[130], which may contribute towards the generation of cytokine storm. This uncontrolled burst of cytokine release by the immune system in response to SARS-CoV-2 infection results in generation of 'cytokine storm' (increased release of proinflammatory cytokines) and thereby aggravate the symptoms of sepsis and contributed towards death of severe COVID-19 patient[28]. Cytokine storm is something like 'Cloudburst' leading to unexpected heavy rain causing devastating damages. Perhaps, the "cytokine storm" is the most lethal and potentially life-threatening episode in relation to COVID-19 (Figure 3).

ARDS is the major cause of respiratory failure leading to over 70% deaths of COVID-19 patients.

In general, the lung infections are cleared by recruiting set of immune cells, such as macrophages and monocytes that respond to the infection and release cytokines and the adaptive responses by T and B cells progressively recedes and the patients are recovered. More precisely, the initial inflammation attracts the virus-specific T cells at the site of infection and clear the virus infected cells before the spread of virus. Moreover, neutralizing antibodies can block the viral infection while the alveolar macrophages recognize the apoptotic cells and neutralize viruses and eliminate them by a process of phagocytosis[28]. However, the dysfunctional immune response induces a cytokine storm that results into widespread lung inflammation (Figure 3). The evolving clinical observations indicate that the COVID-19 patients requiring ICU admissions exhibited higher levels of cytokines, such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IFN-γ, G-CSF, MCP1, TNF-α and chemokines like CCL2, CCL3, CCL-5, IP-10 which all collectively contribute to the causation ARDS and multiorgan damage/failure mostly to heart, kidney and liver[26,28,123,127,131] (Figure 3).

The most notable pathophysiological adverse effects of pro-inflammatory cytokines include shocks and tissue damage in the heart, kidney and liver (elevated levels of ALT, AST, γ-GT), respiratory failure and multiple organ failure. The pro-inflammatory cytokines also induce extensive pulmonary adversities leading to massive infiltration of macrophages and neutrophils, diffuse alveolar tissue damage along with diffuse thickening of the alveolar wall. Lymph node necrosis and spleen atrophy were also observed due to cytokine burst in deceased patients[128]. The inflammatory cytokines may also activate the T-helper type 1 (Th1) cell response as it happens to be a key event in the activation of specific immunity. Interestingly, unlike SARS patients, COVID-19 patients have elevated levels of Th2 cell secreted IL-4 and IL-10 cytokines, which per say are involved in inhibition of inflammatory response. The serum levels of these cytokines are positively correlated with the severity of COVID-19[132]. In a prospective cohort study of 179 COVID-19 patients integrating the age-, sex-, and preexisting comorbidities, the population of $CD3^+$ and $CD8^+$ T-cells (≤75 cells·μL^{-1}) was one of the prominent predictors of high mortality in COVID-19 pneumonia patients[133] (Figure 3).

As a part of the virus replicative cycle, cytopathic viruses (including SARS-CoV-2) are known to induce the injury and death of virus-infected cells. More precisely, viral replications in airway epithelial cells may induce high levels of virus-associated pyroptosis and vascular leakage. The virus induced pyroptosis and vascular damage were observed in patients with SARS-CoV[134]. Pyroptosis is likely to trigger inflammatory responses wherein IL-1β, an important marker cytokine of pyroptosis, is increased during SARS-CoV-2 infection[26]. SARS-CoV-2 also infects the circulating immune, such as CD3, CD4, and CD8 T cells and increases apoptosis of lymphocytes which ultimately leads to lymphocytopenia[28,127,128]. Although no SARS-CoV-2 gene expression has been reported in PBMCs of COVID-19 patients, however, the pathological processes like autophagy, apoptosis, and p53 pathways have been reported to be upregulated in PBMCs of COVID-19 patients[135]. Few clinical investigations also suggested the functional exhaustion of $CD8^+$ T and NK cells with upregulation of NKG2A in COVID-19 patients, which perhaps could be restored after recovery from viral infection[136].

Subsets of T cell mediated immunity plays a key role in clearing virus infected cells. In a cohort study of 452 COVID-19 patients from Wuhan, China, it was observed that the Th cells like CD3+, CD4+ and T suppressor cells like CD3+, CD8+ were found below the threshold levels with a progressive decline in Th cells in severe patients; however the Th and suppressor T ratio (Th/Ts) were in the normal range. In fact, the differentiation of naive CD4+ T cells into memory and effector cells is one of the most fundamental process in T-cell mediated immunity. The study demonstrated a greater number of naive CD4+ T-cell subpopulations and lesser number of memory cells in critical COVID-19 patient, indicating impaired immunity in severe cases. The study also reported lower levels of subsets of regulatory T cells, such as CD3+, CD4+, CD25+, CD-127low+ in severe COVID-19 cases. There was substantial decline in naive (CD45RA+, CD3+, CD4+, CD25+, CD127low+) and induced regulatory T cells (CD45RO+, CD3+, CD4+, CD25+, CD127low+) in critical COVID-19 patients[127]. Germinal center formation is driven by B cell secreted IL-6 and patients having impaired physiological immune response, the B cell generated IL-6 may leads to increasing the level of inflammation[137]. The impaired immunity is demonstrated in COVID-19, however, the role of B cell generated IL-6 in COVID-19 is yet to be investigated.

Improving the immune functions has remained a major thrust area in the mainstream of

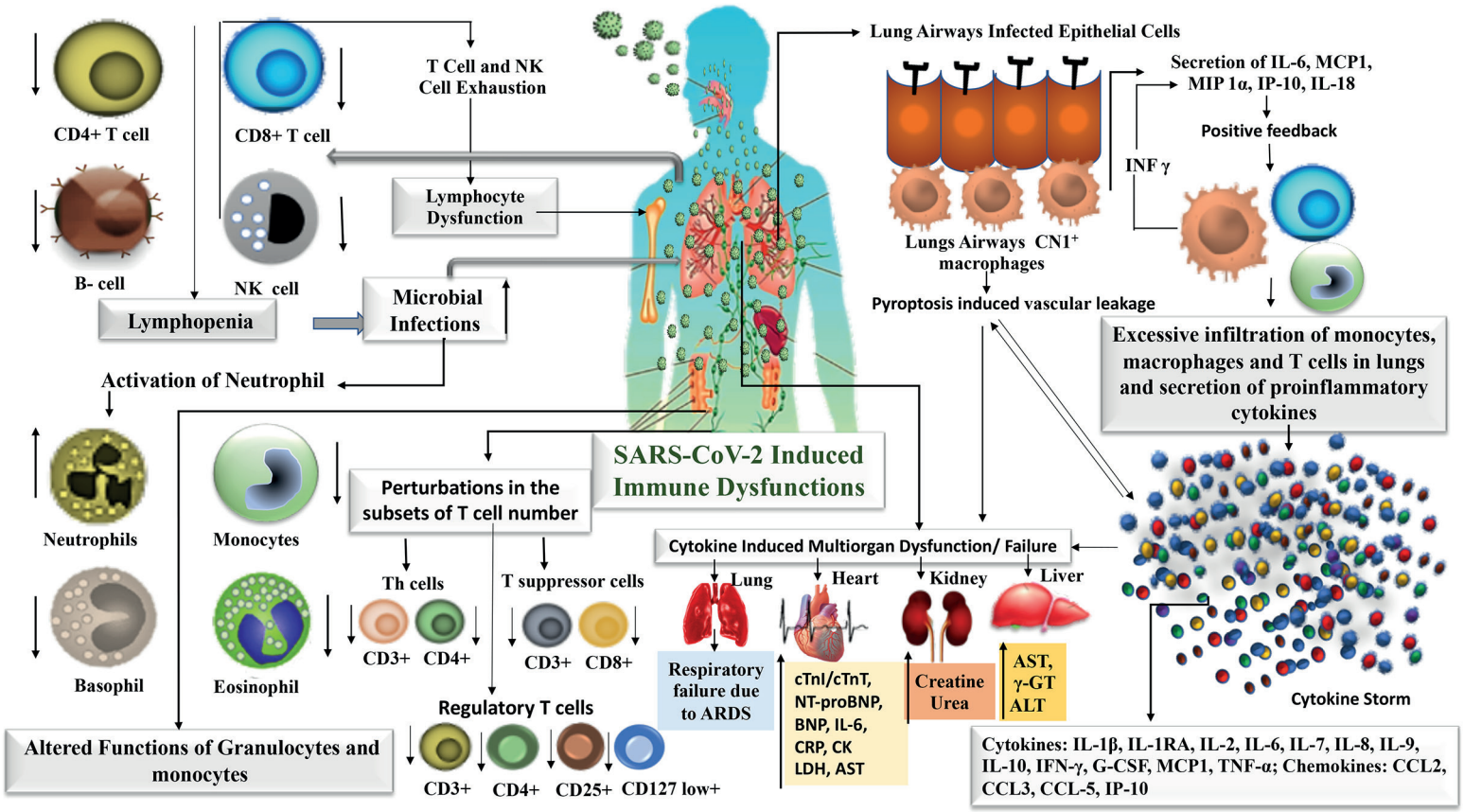

Figure 3. Dynamics of immune functions in COVID-19. The drastic reduction in CD4+ T cells, CD8+ T cells, B-cells and NK cells leads to lymphopenia which increases the possibility of microbial infections and thereby recruit and activate the neutrophil functions. The population of subsets of T cells like Th cells (CD3+, CD4+), T suppressor cells (CD3+, CD8+) and T regulatory cells (CD3+, CD4+, CD25+, CD125low+) are reduced significantly in COVID-19. Lymphocyte dysfunction is linked with T and NK cell exhaustion in COVID-19 patients. On the other hand, SARS-CoV-2 infections perturb the functions of other granulocytes like basophils, eosinophils and monocytes. During the progressive COVID-19 episode, there occurs successive infiltration of immune cells in lung airways. The infiltrated immune cells (macrophages, T cells, monocytes) along with alveolar epithelial cells secretes a panel of proinflammatory cytokines and chemokines (Cytokines: IL-1β, IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IFN-γ, G-CSF, MCP1, TNF-α; Chemokines: CCL2, CCL3, CCL-5, IP-10) which enters in circulation due to cytokine induced cell pyroptosis leading to vascular leakage. The cytokine storm induces variety of dysfunctions in body organs like lungs, heart, kidney and liver which ultimately leads to multiorgan failure. Series of dysfunctional biomarkers of heart (cTnI/cTnT, NT-proBNP, BNP, IL-6, CRP, CK, LDH, AST), kidney (creatine, urea) and liver (AST, γ-GT and ALT) are elevate in critical COVID-19 patients.

COVID-19 management. As a part of tailoring therapeutic strategy against damaging effects of cytokine storm, the immunosuppressing corticosteroids are tested with a hope of amelioration the lung damage and reducing disease progression to respiratory failure leading to death. Interestingly, an outcome of a randomized clinical trial 'RECOVERY' demonstrated the reduction in mortality by about one-third COVID-19 patients who were on ventilators and receiving dexamethasone at a low-to-moderate dose of 6 mg/per day up to 10 days[138]. Impressed with the results, the U.K. government has approved dexamethasone and granted permission to State-funded National Health Service (NHS) for its clinical use in the management of COVID-19. Although the results of dexamethasone treatment are encouraging, however, there are no global consensus over the use of dexamethasone or steroids as it adversely affects the protective function of T cells, inhibit B cells from producing antibodies, inhibit macrophages from clearing secondary/nosocomial infections and perhaps leading to increased plasma viral load that may sustain for a longer duration. Therefore, dexamethasone interventions may be useful as short-term therapeutic strategy in critical COVID-19 patients, but may prove outright dangerous during recovery phase, since the virus will not only remain in the body, but it will prevent generating protective antibodies against SARS-CoV-2[139].

Another immunotherapeutic approach practiced in many parts of the world is the transfusion of convalescent plasma samples (plasma therapy) from recovered COVID-19 patients. Convalescent plasma samples are transfused in COVID-19 patients and it has apparently good clinical outcomes in many parts of the world. However, a systematic review analysis[140] revealed that there is no certainty about the beneficial effects of convalescent plasma to hospital admitted COVID-19 patients and of the controlled studies, none of the study reported on positive outcome in the control arm. The authors also concluded that a very low-certainty evidence towards the safety of convalescent plasma for COVID-19 patients. Moreover, some of the adverse effects of plasma transfusions can be attributed with allergic reactions, mild fever, fatal bronchospasm, transfusion related to acute lung damage and circulation overload especially in patients having cardiorespiratory comorbidities etc. Under such circumstances the clinical application of plasma therapy warrants careful and rational approach of using plasma transfusions for management of COVID-19. In the current situation, there is very limited data pertaining to adverse effects of plasma therapy[131,140].

Conclusions

It has been said that 'extraordinary times may call for extraordinary measures' perhaps this proverb relates with the efforts that are being undertaken for the management of COVID-19. Across the world the clinical presentations of COVID-19 are diverse and ranging from asymptomatic, mild symptoms to critical or severe illness and mortality. Nevertheless, the upcoming novel clinical presentations and pathophysiological findings are evolving. This review has presented an overview of worldwide preexisting comorbidities linked mortality and morbidity profile of COVID-19 patients. We have also attempted to answer few questions like why the levels of ACE2 expression are instrumental in SARS-CoV-2 infection and how it acts as an angel or demon in different comorbid diseases of COVID-19. We also tried to compile a literature for answering a question like why COVID-19 patients having history of cardiovascular comorbidities, hypertension and diabetes should be more cautious and alert towards SARS-CoV-2 infection. The major predictive biomarkers of cardiovascular functions, vascular thrombosis, diabetes and hypertension have been discussed in the light of upcoming clinical data from COVID-19 cases. An elaborative discussion pertaining to the puzzle of prescribing ARBs and ACEI drugs in treating hypertension in COVID-19 might add to the awareness of common people. We have also discussed the dynamics SARS-CoV-2 induced perturbations in innate and acquired immunity in Covid-19 patients which may rationalize the essence of boosting immune status of individuals for fighting against viral infection. Overall, the literature presented in the present review might contribute towards awareness about the evolving pathophysiology in relation to preexisting comorbidities linking cardiovascular functions, hypertension, thrombosis, and diabetes in COVID-19 patients. Although there is no tailored treatment for the effective management of COVID-19, however the evolving clinical manifestations might inspire the physicians to formulate a personalized treatment modality for COVID-19 patient as Sir William Osler's (1849-1919) has rightly stated that "The good physician treats the disease; the great physician treats the patient who has the disease".

Conflict of Interest

The Authors declare that they have no conflict of interests.

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